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Inflammatory bowel disease — the disease and its diagnosis

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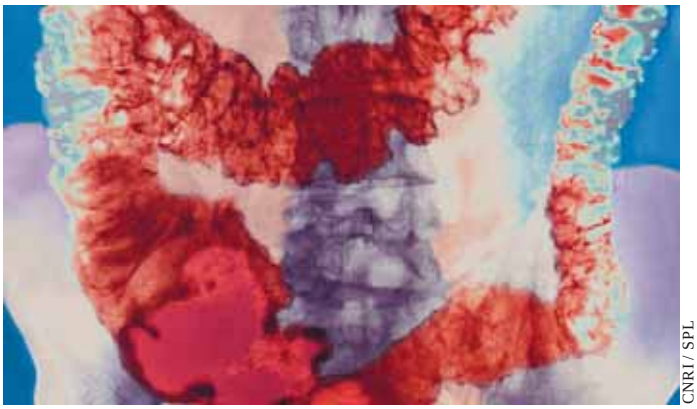
Inflammatory bowel diseases are characterised by chronic, relapsing intestinal inflammation. The first part of this month's special feature sets out the clinical features and diagnosis of ulcerative colitis and Crohn's disease



CNRI / SPL

Part of a coloured barium X-ray of the colon of a patient suffering from ulcerative colitis

Inflammatory bowel diseases (IBD) encompass Crohn's disease (CD) and ulcerative colitis (UC). These are conditions characterised by chronic, relapsing intestinal inflammation. They are believed to result from genetic and environmental factors that act on the immunoregulatory system and cause inflammation of the gastrointestinal mucosa.

UC was first described in 1859 by Samuel Wilks, a physician at Guy's Hospital, London. CD was first described as a chronic interstitial enteritis distinct from tuberculosis by T Kennedy Dalziel in 1913, although it is the later description by Burrill Crohn that gives the disease its name. It was not until the 1960s that there was widespread acceptance that UC and CD were separate diseases.

Epidemiology

Geography and race The incidence of new cases of UC in Europe and the US is 2–8 per 100,000 per year, with a prevalence of 40–80 per 100,000 per year. There is no real evidence of a change in frequency in the past 30–40 years.

In the UK, CD occurs with a similar frequency to UC — the incidence of new cases is about 4 per 100,000 per year, with a prevalence of about 50 per 100,000.[1] Rates in central and southern Europe are somewhat lower. In South America, Asia, and Africa CD is uncommon but appears to be on the rise.

Within geographic areas, ethnic and racial variations exist in the incidence of IBD.[2] CD is three to eight times more common in Jewish than in non-Jewish persons. The incidence among Israeli Jews, however, is much lower than among American and European Jews. In the US, the incidence of both UC and CD in the African-American population has been one-fifth to one-half that in the Caucasian population, but in recent years that gap appears to be narrowing.

Some of the apparent increases in incidence in CD over time may reflect the greater awareness of the disease, better diagnostic studies, and improved reporting. Some patients now diagnosed as having CD may have been diagnosed as having UC in the past. Despite these ambiguities, certain trends are apparent. In geographic areas where the incidence of these diseases has been slight, it is now increasing. In northern Europe and North America, where the incidence of both UC and CD has been substantial, the incidence of UC has levelled, but that of CD is still increasing.

Age and sex UC is more common than CD in children younger than 10 years. The incidence of UC is highest in early adulthood; primarily young adults are affected (20 to 40 years of age) but the disease may present at all ages.

The main peak of incidence for CD is between 15 and 25 years, with a lesser peak occurring between 55 and 65 years in some types of CD. CD can occur in childhood, although the incidence is much lower before the age of 15 years. Most studies have shown there to be an approximately equal incidence of both diseases in males and females, although for CD, some studies show a slight female predominance.

Environmental and behavioural factors Non-smokers have a higher risk of getting UC than current smokers, and stopping smoking can provoke the emergence of UC. However, smokers have a greater risk of getting CD than the general population.[2] They also have a more severe course of CD, require more immunosuppressive drugs and their disease recurs more quickly after surgery. Stopping smoking may moderate the clinical course of CD, although the greatest benefit of cessation is seen with the heaviest smokers. The active ingredients in cigarette smoke that increase the risk of CD have not yet been identified.

Appendicectomy has no influence on the risk of developing CD but strongly protects against the development of UC. Poor sanitation in childhood is a protective factor against the development of CD.

Diet can also play a part. Those who were breastfed as infants have a reduced risk of developing CD and UC. A high intake of simple carbohydrates and fast food increases the risk of developing CD.

Clinical features

Disease location The clinical pattern of UC is based on the extent of colonic

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involvement. If UC affects only the rectal mucosa, it is termed "proctitis". If it extends into the sigmoid colon it is termed "proctosigmoiditis". If other parts of the colon are involved it is termed "colitis" or "pancolitis" (if the whole of the colon is involved).

CD has diverse anatomical locations. This affects how the disease presents, the clinical course and therapeutic options. There are three major patterns of disease distribution,[3] which are set out in Panel 1. Among those with colonic disease, most have pancolitis, but about a third have segmental disease. Much less commonly, CD involves more proximal parts of the gastrointestinal tract, such as the mouth, oesophagus, stomach, and duodenum.

Symptoms and physical findings In UC, the severity of attacks is variable and is closely linked to the extent of colonic involvement. In proctitis, symptoms usually consist of the passage of mucus and blood, with troublesome tenesmus (ie, constant sense of heavy discomfort about the lower bowel and desire to defecate, coupled with straining when doing so), but little diarrhoea. More extensive involvement of the colon causes diarrhoea, which is often bloody. Ulceration, extending deep into the mucosa, can cause pain and fever and can give rise to a risk of bowel perforation.

The predominant symptoms in CD are diarrhoea, abdominal pain and weight loss. Any of these symptoms may be most prominent, in contrast to UC, in which diarrhoea is almost universally the most prominent complaint (except in proctitis) The initial presentation of CD may not be dramatic. Patients may have intermittent symptoms before the diagnosis is considered.

Diarrhoea occurs in almost all persons with CD, but the pattern varies with the anatomical location of the disease.[3] In colonic disease, especially involving the rectum, the diarrhoea is of small volume and associated with tenesmus. Disease confined to the small intestine causes large volume stool production, but no tenesmus or urgency. Severe terminal ileal involvement and previous terminal ileal resection are associated with bile salt diarrhoea which, in severe cases, can result in steatorrhoea (passing of stools containing an excess of fat).

The location and pattern of pain in CD often correlate with disease location. Cramping right lower quadrant pain is a common pattern in patients with ileocolonic disease. This type of pain is caused by stretching of the bowel wall in segments which can lie proximal to areas of narrowed, partially obstructed bowel lumen. Abdominal distension, nausea and vomiting can accompany the pain. Visceral pain is also common in CD, where the serous membrane surrounding the abdomen can be inflamed.

Weight loss of variable degrees occurs in most patients, irrespective of the anatomical location of their disease. Loss of more than 20 per cent of body weight is less common, occurring in 10 to 20 per cent of affected persons. Malnutrition is common in CD, with an incidence ranging from 25 to 80 per cent. Although several factors, such as malabsorption and increased resting energy expenditure in septic or underweight patients, may contribute to malnutrition, decreased oral intake is the primary cause.[4]

Constitutional symptoms contribute significantly to the overall morbidity in CD. Fever and chills often accompany CD activity — indeed, a low-grade fever may be the patient's first warning sign of a flare of activity. Fatigue and malaise can reduce the ability to function markedly and may have a negative impact on work performance.

Physical findings in IBD also vary with distribution and severity of disease. When the disease is active, the patient may be pale, weak and chronically ill. Ulcers in the mouth are more common in active CD, but occasionally these oral lesions may be the presenting feature of the disease. The abdomen may be tender, typically over the area of disease activity. In CD, patients may also have thickened bowel loops, thickened mesentery (ie, peritoneal membrane) or an abscess, which may cause a sense of fullness. Fistulous openings, induration, redness or tenderness near the anus suggest the presence of perianal CD. Fissures may be present in the anal canal, and these may bleed causing confusion with active colitis.

In a severe flare up of IBD, patients may have a fever and tachycardia (of greater than 100 beats/min) and are often in severe pain.

Panel 1: The three major patterns of Crohn's disease distribution

- Disease present in the ileum and caecum, a pattern seen in 40 per cent of patients at presentation
- Disease confined to the small intestine, a pattern seen in 30 per cent of patients at presentation
- Disease confined to the colon, a pattern seen in 25 per cent of patients at presentation

Extraintestinal features

Although UC and CD primarily involve the bowel, both are associated with manifestations in other organ systems. The extraintestinal manifestations may or may not follow the clinical activity of the underlying IBD. Most occur more commonly with UC or CD colitis than with CD confined to the small intestine.

Arthritis The most common extraintestinal manifestation of IBD is arthritis. Historically, two principal patterns of arthritis in IBD have been recognised:

- Peripheral, often asymmetric, colitic arthritis
- Spondyloarthropathy (SpA) resembling idiopathic ankylosing spondylitis (found in 10 per cent of patients with UC and less frequently in patients with CD)[5]

Peripheral arthritis is itself subdivided into three patterns:

- Type I, a peripheral particular arthritis with fewer than five joints involved
- Type II, a peripheral non-symmetric polyarthritis with at least five joints involved
- Type III, an SpA, sometimes with peripheral joint involvement

Type I arthritis may precede the diagnosis of IBD and, once established, often parallels the activity of the intestinal inflammation. Types II and III arthritis do not reflect the activity of the underlying IBD and rarely precede the diagnosis of IBD. Sacroileitis, an inflammation of the joint between the sacrum and the ileum, can be seen in conjunction with ankylosing spondylitis, but more often alone. Over 20 per cent of IBD patients, most of whom have no back pain, have radiologic evidence of Sacroileitis.

Colitic arthritis, uveitis (ie, inflammation of any component of the uveal tract in the eye) and erythema nodosum (ie, red, tender nodules on the shins) are often seen together.

Dermatological manifestations The two most common dermal complications of IBD are pyoderma gangrenosum (small pustules on skin that develop into large ulcers) and erythema nodosum (see above). Pyoderma gangrenosum is seen with colitis and ileocolitis, and is associated with extensive, long-standing disease. The incidence of pyoderma gangrenosum in UC is low (1 to 5 per cent), and it is even lower in CD — however, 36 to 50 per cent of all patients with pyoderma gangrenosum have IBD. The activity of pyoderma gangrenosum may or may not follow the activity of IBD but skin lesions almost always develop during a bout of acute colitis.

Erythema nodosum is seen particularly in children with CD. Activity follows the activity of the bowel disease and responds to treatment of the bowel disease.

Sweet's syndrome (an acute febrile neutrophilic dermatosis), which has some similarity to erythema nodosum, may also be associated with IBD .

Eye complications Ocular complications are infrequent, occurring in less than 10 per cent of cases. Episcleritis (inflammation of the outer-most layer of the eye) is the most common complication of IBD. This

generally occurs during increases of intestinal IBD activity and often resolves with treatment of the underlying IBD. Scleritis, which involves more of the eye, is a more severe ocular disorder than episcleritis because it may impair vision. Uveitis is often associated with joint and skin manifestations of IBD, and can occur during active bowel disease, during quiescent periods, or may precede the diagnosis of IBD. Conjunctivitis is frequently seen in patients with IBD, but is not specific and no true association has been demonstrated.

Hepatobiliary complications The hepatic complications of IBD include fatty liver, pericholangitis (ie, inflammation of the tissues surrounding the bile duct), chronic active hepatitis, and cirrhosis. Pericholangitis is the most common hepatic complication of IBD, with prevalences as high as 50 to 80 per cent reported.

The biliary tract complications are primary sclerosing cholangitis (PSC) and gallstones. PSC is a chronic cholestatic disorder characterised by inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts.[6] It is more frequent in males, and the prevalence of IBD (mostly UC) in PSC is about 70 to 80 per cent. Conversely, about 2 to 7 per cent of UC patients have a diagnosis of PSC.

Cholesterol gallstones occur in patients with ileal disease or ileal resection owing to malabsorption of bile salts and the resultant decrease in the size of the bile salt pool.

Thromboembolic complications Thromboembolic complications with arterial, as well as venous events, occur in about 1 to 2 per cent of patients with UC and CD. IBD patients are often exposed to classical thrombosis risk factors such as immobility, surgery, steroid therapy and cigarette smoke. Pulmonary embolism is the most common cause of death in IBD patients in hospital.[7]

Anaemia Anaemia is a frequent extraintestinal manifestation in IBD. About one-third of IBD patients have haemoglobin levels below 12g/dL. Multiple pathogenic mechanisms often coexist in anaemic patients leading to mixed features anaemia. Chronic intestinal bleeding with iron loss (because of bowel inflammation) causes a microcytic (ie, small red blood cell) anaemia whereas the chronic inflammatory disease can cause normocytic anaemia. Other mechanisms implied in anaemia are folate deficiency (because of malabsorption, inadequate diet, and the side effects of sulfasalazine and methotrexate) iron malabsorption and vitamin B_{12} malabsorption. Vitamin B_{12} and folate deficient anaemia is macrocytic. Azathioprine/6-mercaptopurine and sometimes sulfasalazine and 5-aminosalycilic acid can cause myelosuppression as part of their mode of action.

Panel 2: Classical features of ulcerative colitis and Crohn's disease

Clinical feature	Ulcerative colitis	Crohn's disease
Disease distribution	Diffuse and continuous	Segmental
Rectal involvement	Always (in adults)	Occasionally
Disease severity	Increased distally	Patchy and variable
Ileal involvement	Occasional (termed "backwash")	Often
Disease location in colonic wall	Superficial (ie, outermost layer)	Transmural
Transmural lymphoid aggregates	Rarely found, perhaps underneath ulcers	Any location
Fissures	Rare, but can be found superficially in fulminant colitis	Deep, can be found at any location
Sinuses and fistulas	Absent	Present
Granulomas	Related to ruptured crypts*	Not crypt-related

*Crypts are pitted abscesses characteristic of ulcerative colitis

Complications

In severe UC, toxic dilation implies that inflammation has spread into the muscle layers of the colon and there is an associated high risk of perforation with a mortality of 50 per cent.

Patients with UC and Crohn's colitis carry an increased risk for developing colorectal cancer (CRC). Patients with more extensive colitis, greater duration of disease, concomitant primary sclerosing cholangitis, and a family history of CRC are at greatest risk among UC patients. Young age at disease onset and greater inflammatory burden have also been proposed as risk factors.

Diagnosis

Laboratory findings Laboratory findings in IBD are largely non-specific. The peripheral blood count may reveal an anaemia. A moderately elevated leucocyte count is indicative of disease activity, whereas a marked elevation suggests the presence of an infection or, in CD, of an abscess or other suppurative complication. Thrombocytosis may occur with active disease.

C-reactive protein (CRP) is an acute-phase protein that is produced in large amounts by hepatocytes during an acute-phase response. CRP is an objective marker of inflammation and, in CD its levels correlate well with clinical disease activity. CRP is a less reliable marker of inflammation and disease activity in UC patients, except perhaps for severe, extensive colitis or if there is co-existing infection CRP is raised proportionate to disease activity. The erythrocyte sedimentation rate is usually higher in active colonic disease than in ileal disease. Hypoalbuminaemia is a good indicator of disease severity and malnutrition.

Endoscopy Endoscopic biopsy is considered the gold standard for the detection and quantification of IBD. Endoscopy plays an integral role in the diagnosis, management, and surveillance of disease. The procedure is also useful in distinguishing CD from UC (see Panel 2), defining the patterns, extent, and activity of mucosal inflammation, and obtaining mucosal tissue for histological evaluation, as well as in excluding other causes. In established IBD, endoscopy helps define the extent and severity of intestinal involvement, which in turn influences medical and surgical decisions, aids in targeting medical therapies, and allows for the management of IBD-related complications. Furthermore, endoscopy plays a key role in the surveillance of patients with long-standing colitis who are at increased risk for dysplasia and the development of colorectal cancer. Recent advances include the use of wireless capsule endoscopy.

Histopathology Features that strongly indicate that a patient has CD (rather than UC) are the presence of chronic active inflammation of the ileum, deep fissuring ulcers that extend into the outer aspects of the muscular coat of the intestinal wall, involvement of just segments of the colon in a patient who has not undergone previous surgery, and the presence of epithelioid granulomas unassociated with ruptured crypts (pitted abscesses).[8] In addition, CD inflammation runs deep into the layers of the intestine in distinction to UC where it rarely breaches the muscularis mucosa (ie, the layers close to the lumen). As a consequence, strictures, fissures and fistulae are hallmarks of CD.

Several other inflammatory disorders, such as certain bacterial or parasitic infections, radiation injury and ischaemia, may mimic the histological appearances of UC or CD in biopsy or resection specimens.

Radiology Radiological imaging is complementary to the clinical and endoscopic assessment of the patient. Radiological imaging studies are used in the initial evaluation of the patient for the purpose of establishing a diagnosis, in the preoperative situation to verify the full extent of the disease, during clinical exacerbations to

determine if complications are present, and to evaluate extraintestinal manifestations of IBD. For the small bowel, as well as for extraintestinal complications, radiological imaging still plays a key role in established IBD, whereas conventional X-ray examinations of the colon have largely been replaced by endoscopy.

CT and MRI are the best radiological methods for detecting extraluminal disease, such as abscesses and fistulae. However, only severe colonic inflammation in patients with CD can be sufficiently visualised by CT and MR colonography (MRC). MRC can be considered a promising alternative to endoscopic biopsy in monitoring IBD activity or assessing therapeutic effectiveness.

Aetiopathogenesis

Genetic factors Epidemiological and linkage studies suggest that genetic factors play a significant role in determining IBD susceptibility. Twin studies support the presence of a genetic basis for both CD and UC. The concordance rate of CD in monozygotic twins (44.5 per cent) is greater than for dizygotic twins (3.8 per cent). In UC, the concordance rate for monozygotic twins is 10 per cent. Approximately 15 per cent of patients with IBD have first-degree relatives who also have IBD. Lifetime individual risk is 8.9 per cent for siblings, and 3.5 per cent for parents. The incidence of disease among first-degree relatives is higher in CD than in UC. The incidence of IBD among first-degree relatives of IBD patients is 30 to 100 times the general population. Although the relatives of patients with CD are more likely to have CD than UC, the incidence of ulcerative colitis in this group is also higher than in the general population. Similarly, relatives of patients with UC have a higher incidence of both UC and CD than the general population. These data support that CD and ulcerative colitis are related diseases. But the CD in families with mixed diseases is usually colonic.

There is an association of CD with subclinical markers that exhibit familial aggregation. An example of this are serum antibodies to the yeast *Saccharomyces cerevisiae* (ASCA), which are directed against cell wall oligomannosidic epitopes and have a sensitivity of 50 to 60 per cent and a specificity of 80 to 95 per cent for differentiating CD from controls. Studies have also reported the production of ASCA by a fraction of unaffected relatives of CD patients.

In UC, the most consistent genetic associations have been shown for the MHC locus HLA Class II alleles, but the interleukin-1 family of genes and the multidrug resistance gene, MDR1, have also been implicated as genetic susceptibility factors for the development of disease.

Linkage studies have implicated several genomic regions as likely to contain IBD susceptibility genes, with some observed uniquely in CD or UC, and others common to both disorders. The best replicated linkage region, IBD1, on chromosome 16q contains the CD susceptibility gene, NOD2/CARD15.[9] This is expressed in peripheral blood monocytes and three major coding region polymorphisms within it are associated with CD among patients of European descent. Having one copy of the risk alleles confers a 2- to 4-fold risk for developing CD, whereas having two copies increases the risk 20- to 40-fold. Carriage of NOD2/CARD15 risk alleles is associated with early onset CD of ileal location and the presence of strictures. Other IBD genomic regions include IBD2 on chromosome 12q (observed more in UC), and IBD3, containing the major histocompatibility complex region. A short genomic region has been associated with CD on chromosome 5q, but the precise contributing gene is as yet unidentified.

Bacteria The normal human large intestinal microflora is made up of a complex ecosystem of at least 500 species of bacteria. Bacterial flora are known to affect the development, structure and function of the mucosal immune system and have a conditioning effect on mucosal integrity.

The evidence for the role of enteric bacteria in the pathogenesis of CD is substantial, although no specific infectious agent has been conclusively identified. It has been shown that CD patients display an increased number of coliforms in their faeces, particularly during periods of active disease. Immunocytochemistry has documented the presence of *Escherichia coli* antigens in most intestinal resection specimens from CD patients. Increased numbers of *E coli* in the intestinal mucosa have been observed in patients with IBD, compared with asymptomatic controls.[10] Increased luminal concentrations of *Bacteroides* spp, *Eubacterium* spp, *Peptostreptococcus* spp *and Coprococcus* spp have been reported in CD patients, and increased concentrations of anaerobic bacteria such as *Steptococcus faecium* has been reported in UC patients. In addition, *Listeria monocytogenes* antigens have been detected in 75 per cent of patients with CD, but in only 13 per cent of patients with UC, and not at all in control patients. It is, however, not clear whether there is a causal relationship between *Listeria monocytogenes* and CD. Ever since T Kennedy Dalziel, first published a detailed description of chronic enteritis in humans in 1913, the potential involvement of *Mycobacterium paratuberculosis* in CD has remained controversial.

Management

The pharmacological management of IBD is discussed in detail in the second part of this special feature (p161–6). In addition to drug treatment, a flare up of IBD can require dietary input, intravenous hydration (with or without electrolyte replacement), pain management, prevention of thrombosis and, if there is severe anaemia, blood transfusion.

Surgery is reserved for patients who have developed complications. These include toxic dilation and, in CD, abscesses, fistulating disease, strictures causing bowel obstruction, perianal disease or CRC.

Conclusion

There is no simple cause and effect relationship to explain most cases of IBD — instead, a complex interaction of environmental and behavioural factors (such as diet and smoking habits) and genetic factors is involved.

Diagnosis also remains inexact, but has been aided by some recent advances in strategies. These include the detection of faecal and serologic markers (such as C-reactive protein) and the use of wireless capsule endoscopy.

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